I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claim 11 has been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner suggests that this claim is drawn to a compound which hybridizes with an active site which is not defined in a way in the specification that allows one to understand how it is experimentally determined. Applicants have canceled claim 11. Withdrawal of this rejection is respectfully requested.

Claims 15-20 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification while being enabling for antisense inhibition of phospholipid scramblase 1 expression *in vitro* does not reasonably provide enablement for *in vivo* antisense inhibition of expression of phospholipid scramblase 1; the Examiner cites several articles to support this position. Applicants respectfully traverse this rejection of the claims.

Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* is highly unpredictable.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans. f studies presented in the instant specification. Therefore, what these papers cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the references cited do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The paper by Braasch and Corey (2002) describes the advances that have been made in the design of antisense compounds over the years. Included in the discussion are the types of advances that are taught in the specification as filed. Nowhere in the reference

do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*. In fact, the paper states in the abstract that success in clinical trials with these agents has occurred.

The paper by Tamm et al. (2001) is another more recent review of the antisense technology and its specific application to oncology. Again, although the use of antisense is discussed in terms of what can go wrong, the paper again describes advances such as those taught in the instant specification. Nowhere in the reference do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The papers by Gewirtz et al. (1996) and Agrawal (1996) are older papers not relevant to the state of the art of antisense compounds in 2001, the filing date of the instant application. Both papers discuss in general terms issues that were related to

older antisense technology. However, nowhere do these papers state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

However, Applicants have amended claim 15 to recite that the method is performed *in vitro* in an earnest effort to advance the prosecution and facilitate the allowance of this case. Claims 16-20 have been canceled with Applicants reserving the right to file a continuing application directed to this subject matter without prejudice. Withdrawal of the rejection is requested in light of these amendments.

II. Rejection of Claims Under 35 U.S.C. 102/103

Claims 1 and 2 have been rejected under 35 U.S.C. 102(b) and 103(a) as being anticipated and/or made obvious by Zhou et al. (1997) or Weidmer et al. (US Patent 6,204,035). The Examiner suggests that both references teach PCR primers that are engineered to bind phospholipid scramblase 1 and thus would specifically hybridize with phospholipid scramblase 1 because it is essentially identical in sequence to the applicant's claim. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended claim 1, and by dependency claim 2, to recite that the compounds of the instant

invention are targeted to specific regions within the sequence of phospholipid scramblase 1 of SEQ ID NO: 3, regions that do not include the start codon or stop codon region. Support for these amendments to the claims can be found throughout the specification as filed but in particular at pages 82-85.

Zhou et al. (1997) discloses the cloning of human phospholipid scramblase 1 from human leukemia cells. In the paper, the authors discuss use of two PCR primers that would by their nature bind to the sequence of human scramblase 1. The two primers were targeted to the start codon region and the stop codon region of full-length phospholipid scramblase 1. Nowhere does this paper teach or suggest antisense compounds as claimed that are targeted to specific regions of the human phospholipid scramblase 1 of SEQ ID NO: 3.

Weidmer et al. (US Patent 6,204,035) discloses the sequence of human phospholipid scramblase 1 and also the same PCR primers that were disclosed above by Zhou et al. (1997). The two primers are again targeted to the start codon region and the stop codon region of human phospholipid scramblase 1. Nowhere does this paper teach or suggest antisense compounds as claimed that are targeted to the specific regions of the human phospholipid scramblase 1 of SEQ ID NO: 3 as recited in amended claim 1.

Under both 35 U.S.C. 102(b) and 103(a), in order to establish anticipation or obviousness, the cited references must teach the invention of the cited claims by teaching its limitations. Neither cited reference discloses antisense compounds that are targeted to the claimed regions of human phospholipid scramblase 1 of SEQ ID NO: 3 and thus cannot anticipate or make obvious the invention of the amended claims (MPEP 2131 and 2143). Accordingly, withdrawal of this rejection is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Weidmer et al. or Zhou et al., in view of Baracchini et al. (US Patent 5,801,154). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to use the cDNA sequence of Zhou et al. or Weidmer et al. to generate antisense sequences for inhibition of phospholipid scramblase 1 expression and then incorporate the claimed modifications as taught by Baracchini et al. The Examiner suggests that one of skill would have motivated by Weidmer et al. in teaching that the cDNA sequence can be used to create antisense sequences and that inhibition of thrombosis, clot formation or cell clearance could result, while Baracchini et al. teach that

modification of antisense is desired. The Examiner suggests that an expectation of success is provided by the fact that Weidmer teaches that formation of antisense compounds from a cDNA sequence is routine. Applicants respectfully traverse this rejection.

At the outset, claim 1 and its dependent claims have been amended as discussed *supra* to recite antisense compounds targeted to specific regions of human phospholipid scramblase 1 of SEQ ID NO. 3.

As discussed *supra*, Zhou et al. and Weidmer et al. fail to teach or suggest antisense compounds as claimed which are targeted to specific regions of human phospholipid scramblase 1 of SEQ ID NO: 3, specific regions other than the start codon or stop codon regions. Therefore, these primary references fail to teach the limitations of the claims, either alone or when combined with other references cited.

The secondary reference cited fails to overcome the deficiencies in teaching of the primary references.

Baracchini et al. (US Patent 5,801,154) teaches methods of modifying antisense oligonucleotides to enhance activity. However, nowhere do this parent teach or suggest antisense oligonucleotides 8 to 50 nucleobases in length targeted to human phospholipid

scramblase 1 of SEQ ID NO: 3, or any region of such a nucleic acid molecule.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims as amended, which claim antisense compounds targeted to specific regions of human phospholipid scramblase 1 of SEQ ID NO. 3, and thus cannot render the instant claimed invention obvious. Further, the reference of Weidmer et al. does not teach use of any specific antisense compound to inhibit expression of the human phospholipid scramblase 1 gene, and thus fails to provide one of skill with a reasonable expectation of success as asserted by the Examiner. It is only with the specification in hand that one of skill would understand how to make and use the claimed antisense, in particular what regions of the gene to target with antisense as now claimed. Withdrawal of this rejection is therefore respectfully requested.

Attorney Docket No.: RTS-0147
Inventors: Bennett and Wyatt
Serial No.: 09/828,344
Filing Date: April 5, 2001
Page 11

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **February 3, 2003**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 11 and 16-20 have been canceled without prejudice.

Claims 1 and 15 have been amended as follows:

1. (amended) A compound 8 to 50 nucleobases in length targeted to a 5'-untranslated region, a coding region, or a 3'-untranslated region of a nucleic acid molecule encoding human Phospholipid scramblase I (SEQ ID NO: 3), wherein said compound specifically hybridizes with one of said regions and inhibits the expression of human Phospholipid scramblase I.

15. (amended) A method of inhibiting the expression of Phospholipid scramblase I in cells or tissues comprising contacting ~~said~~ cells or tissues *in vitro* with the antisense compound of claim 1 so that expression of Phospholipid scramblase I is inhibited.